PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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RE: Document 2015-21756, *Federal Policy for the Protection of Human Subjects* (80 *Federal Register* 53931)

Dear Dr. Menikoff:

Public Responsibility in Medicine and Research (PRIM&R), a nonprofit organization dedicated to advancing the highest ethical standards in research, appreciates the opportunity to comment on the proposed revisions to the Federal Policy for the Protection of Human Subjects.

Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

We applaud the effort, led by the Office for Human Research Protections (OHRP), to modernize the "Common Rule." However, we do not believe that *as a whole* the proposed regulatory changes will achieve the stated goals of "decreasing administrative burden, delay, and ambiguity for investigators, institutions, and IRBs, and strengthening, modernizing, and making the regulations *more* effective in protecting research subjects" (DHHS 2015, 53942) (Question 1).

I. Introduction

An effective human research protections system is one that safeguards the rights and welfare of all those who participate as research subjects, engenders public confidence in the research enterprise, and builds a partnership with researchers who are ultimately responsible for the conduct of research. Some aspects of our current regulatory framework do not further these aims; clearly, change is necessary. We therefore support federal efforts to "modernize" and "recalibrate" the regulations to better align them with today's research environment. Indeed, the

notice of proposed rulemaking (NPRM) for revisions to the Federal Policy for the Protection of Human Subjects represents an impressive attempt on the part of OHRP to convene and coordinate the Common Rule agencies in response to mounting public criticism and in order to effect this change.

However, PRIM&R's analysis of the NPRM reveals many serious shortcomings. The NPRM includes proposals that reflect inadequate consideration of important ethical, practical, and logistical implications, for example those related to the requirement for "broad consent." Key proposals, such as the mandate for single IRB review, rest on a scant evidence-base and apply untested theories. For a regulatory initiative aimed primarily at streamlining research review and reducing administrative effort, the NPRM proposes rules that risk replacing one set of burdens with another (Question 1).

To be sure, some existing problems, such as the current requirement for at least annual re-review of all approved, ongoing research, derive from the over-interpretation of existing regulations in official "guidance"; in such cases, regulatory change will certainly provide relief from burdens that distract institutional review boards (IRBs) from other, more important tasks. However, the NPRM too often offers new regulatory mandates when more flexible and less permanent solutions outside a regulatory framework would be sensible alternatives.

We also note that the rulemaking process has not been transparent or informed by existing, independent expertise. Legitimate concerns about governmental bias and conflict of interest have emerged throughout the process, as the proposals in the NPRM have been developed out of public view by agencies that themselves conduct and fund research. Even independent expert bodies, such as the Secretary's Advisory Committee on Human Subject Protections (SACHRP) to the Secretary of Health and Human Services (DHHS) and the Presidential Commission for the Study of Bioethical Issues, were not participants in proposal development.

Finally, it is generally understood that those charged with promulgating the final rule are expected to culminate their work prior to the next presidential election. PRIM&R believes that the NPRM is far too unfinished a document to attempt completion within this timeframe. The document provides promissory notes for templates, tools, and procedures that are at the core of its most significant proposals. By posing questions for public comment such as, "Is mandated single IRB review for all cooperative research a realistic option at this time?" the NPRM reveals itself to be a proposal in which even basic matters remain unresolved (DHHS 2015, 53984). In light of these problems, we do not believe efforts to finalize the NPRM as currently written should move forward.

Two distinct and commonly held views appear to be rushing the effort to turn the NPRM, with its many unanswered questions and evident drafting problems, into a final rule. The first is the view that regulatory change is nearly impossible and that needed revisions will not be

adopted for another 25 years if we do not seize the current opportunity. The second is the belief that the current regulatory framework is so completely broken that waiting any longer for change will do harm to the research enterprise. We believe these are precisely the wrong conclusions to draw from the history of the Common Rule and the current state of affairs.

It took a decade for the Common Rule to come into being, from 1981, when the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended that the federal agencies that sponsor research with human beings agree on a single set of rules and procedures, to 1991, when an interagency coordinating body promulgated the Common Rule. Over the past 25 years, the difficulty of getting all of the agencies to agree on the Common Rule was cited as the grounds for concluding that changing any provisions would require a Herculean effort. It may well be that revising the entire Common Rule at once is a task that can only be undertaken once in a generation.

But if the current NPRM, issued four years after the ANPRM to revise the Common Rule (July 26, 2011), underlines how daunting a comprehensive revision can be, it also shows that the best, evidence-based revisions will not emerge from a process that tries to make all needed revisions at once. By perpetuating the view that regulations cannot be revised when needed, the current approach risks locking in place for another 25 years a number of provisions in the NPRM that even its most enthusiastic supporters admit are flawed in important ways.[1]

Instead, we recommend that the relevant agencies pursue an issue-by-issue approach in which it is possible to "drill down" on an issue, to consider all the sections of the regulations where it arises and all the evidence that is available—and that is needed—to resolve it well. Further, the agencies should address each issue more openly, developing and relying upon evidence, and allowing consensus to emerge and revisions to be crafted that will work well for all stakeholders. This approach would not only produce better results, but would signal that, once adopted, any provision can be changed if it does not work as well as intended.

In the following, we describe our specific concerns related to the most significant proposals in the NPRM, as well as one proposal that is notably absent from the NPRM related to investigator responsibilities. We also propose alternative ways forward that reflect a more incremental approach to revising the Common Rule with opportunities for study and input from stakeholders along the way.

II. Research with Biospecimens

Perhaps the most significant change in the NPRM is the expansion of the definition of "human subject" to include: "…a living individual about whom an investigator (whether professional

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[1] Emanuel, Ezekiel. "Reform of Clinical Research Regulations, Finally." *The New England Journal of Medicine.* 373.24 (2015): 2296-2299.

or student) conducting research…(iii) obtains, uses, studies, or analyzes biospecimens" [§__.102(e)]. This proposal represents a substantial departure from the current rule, under which individuals whose biospecimens, obtained either for research or for the purpose of diagnosis or treatment, are not subject to regulatory protection once those biospecimens are de-identified. The research "use, study, and analysis" of such biospecimens therefore occurs without the knowledge or consent of the individuals from whom the biospecimens are derived. The re-definition of human subject research in the NPRM represents an effort to respect the autonomy interests of such individuals, as research with human subjects requires consent. However, because requiring specific consent would create heavy burdens on researchers and barriers to the research use of banked clinical biospecimens, the NPRM requires only a one-time "broad consent," which would permit unspecified future research use of biospecimens collected initially for research as well as those collected in the context of care and treatment. Broad consent is to be discussed and documented using a written form, a template for which will be provided by the Secretary of the DHHS, and the permission for research use of biospecimens would extend for up to 10 years. Research authorized by such broad consent would be exempt from IRB review, provided that privacy safeguards are in place and there has been a limited, one-time IRB review of the broad consent process [§__.104(f)]. Finally, the NPRM puts in place new criteria designed to ensure waivers of informed consent for biospecimens research will be granted only in very rare circumstances. [§__.116(f)].

PRIM&R has identified substantial ethical, conceptual, and practical problems with these proposals and recommends that the regulations in this domain not be changed at this time, in order to allow further study of alternatives.

Principal among the forces driving the NPRM proposals, according to the preamble, are people's autonomy interests in the research use of their biospecimens—that is, the desire of individuals to know about, give permission for, and have some control over future research with biological materials collected from them.

PRIM&R supports efforts to remedy a significant limitation of the current regulatory framework, namely, that the Common Rule does not apply once a biological specimen is stripped of identifying information. In the research setting, specimens are obtained from subjects and used by researchers in accordance with procedures specified in the consent document. It seems at odds with the basic notion of respect for persons that a researcher may then remove identifiers from specimens, effectively rendering void the "agreement" between researchers and research subjects represented by that consent, and use the specimens at will. The fact that research use of specimens obtained from patients in the clinical context for the purposes of care and treatment is unregulated once identifiers are removed also seems to controvert the principle of respect for persons.

Thus, the NPRM begins from the correct premise, namely, that the gaps in the current regulations ought to be filled. It does not follow, however, that the rules proposed in the NPRM regarding research use of biospecimens represent an improvement over the current regulations.

First, recent empirical studies suggest that people care about their biological materials and how they may be used, even when identifying information has been removed. It is worth noting, however, that whether and to what extent people's desires and preferences should be used to determine policy is subject to significant debate. At the very least, data must be validated and broadly applicable if it is to drive regulation, which is not true of the current literature. For example, while research indicates that subjects consistently express a desire to be asked permission for the use of their biospecimens, it does not address how such opinions evolve over time or vary in different contexts (for example, against a background of greater trust in research) or when questions about preferences are framed in terms of trade-offs (for example, if respondents understood that an opt-out procedure rather than consent would increase research participation). A new Common Rule should not rely so narrowly on what may be short-lived attitudes and expectations regarding consent, the sharing of information, and the research use of biological specimens. Enduring ethical obligations of the sort codified in the Common Rule should not vary based on changes in public opinion.

Second, the broad consent approach proposed is not likely to engage people at a time and in a way that offers them meaningful choice about use of their biospecimens. The purpose of an informed consent process or mechanism in the context of research is to enable individuals who are being asked to participate in research to make informed decisions about whether it is in their interest to do so, given the nature and goals of the research and its potential harms and benefits. It is unclear how a consent process can amount to much more than a general notification procedure when individuals are asked to agree to have their biological specimens used for future unspecified research when even the purpose of the research and the specimens involved are unknown. Calling this "consent" devalues that core concept in bioethics, and the process envisioned would only minimally satisfy the ethical premise of autonomy (Question 54).

Moreover, in the patient care context, broad consent would usually be obtained when individuals are entering a clinical facility and are asked to review and complete a sheaf of required forms, contracts, and notices, such as verification of identity, assignment of benefits, acceptance of financial liability, advance directives, patient bill of rights, notice of institutional privacy practices, and informed consent for treatment, among others. The staff who handle such paperwork would not be those familiar with research or best equipped to answer patients' questions about the nature, potential risks, or potential benefits associated with biospecimen research. Again, this is "consent" in name only.

Third, whether fewer individuals will agree to take part in research under the circumstances described above is simply not known. What seems certain, however, is that obtaining broad consent as outlined in the NPRM is impracticable and threatens to put a halt to important research. While the stated goal of the NPRM is to reduce unnecessary administrative burden associated with regulation, the requirements related to the use of biospecimens in research will likely create new barriers to research participation without advancing subject autonomy. New systems and mechanisms for obtaining and tracking broad consent across all patients entering a facility will need to be developed and implemented. This process will require significant resources on the part of institutions that collect biospecimens; it will be entirely out of reach for small healthcare institutions and community and school-based clinics, and may very well be beyond the capability of some larger and better-resourced institutions. As some facilities decide that they cannot manage the costs (in terms of time, staff, infrastructure, and other resources) of obtaining and tracking broad consent (is the consent still valid? does it impose any limits or requirements regarding the use of an individual's specimens? etc.), specimens collected for clinical purposes at such facilities will no longer be available for future research. As a result, the populations within the communities those institutions serve may be excluded from such research. This is problematic from the perspectives both of justice and of good science (Question 54).

Fourth, an illogical asymmetry exists between the way the NPRM treats biospecimens, on the one hand, and personal information and data, on the other. The NPRM requires consent for research involving biospecimens, whether currently identifiable or not and whether collected for research or non-research purposes. With respect to research use of private information, the NPRM proposes less stringent standards. As is the case under the current rule, secondary research use of *non-identified* private information would not require consent, even though researchers have shown that modern analytic methods make it possible to identify individuals in anonymized data just as it is possible in anonymized biospecimens.

Nor is consent required for secondary research use of *identifiable* private information if the information was collected for non-research purposes, provided that privacy safeguards are in place and prior *notice* of such use is given to the subjects. If identifiable private information is being collected for future research or for storage for such use, then, as with biospecimens, broad consent is required, but, unlike biospecimens, it can be obtained via oral consent. Finally, while the NPRM aims to make waivers of consent in the case of research use of biospecimens extremely rare, it makes no changes to the provisions allowing waivers related to secondary research use of identifiable private information, and in fact, supports their use as a mechanism for facilitating important research. Since individuals have legitimate interests related to research use of both their information and biospecimens, the proposed distinction seems arbitrary (Question 66).

Fifth, while the proposed requirement to obtain broad consent may reflect a desire to respect people's interests in controlling the use of their biospecimens, the proposal introduces

restrictions that can produce the opposite result. According to the NPRM, the exemption for secondary research use of biospecimens when broad consent has been obtained at §___.104(f)(2) does not apply to research in which results will be returned to subjects. This means that when research is conducted in accordance with broad consent, an investigator who uncovers clinical information that could be important to a subject's health or welfare would be prohibited from sharing that information with the subject. By not permitting exemption of research that intends to share individual results, the new rules may create an undesirable disincentive. Research rules that endeavor to promote subject autonomy should not place restrictions on the sharing of information with those subjects. Given the vast and evolving nature of research, and the diversity of settings in which consent for biospecimens research would be sought, IRBs, researchers, and sponsors should be permitted to tailor consent rules related to the sharing of results to the nature of the information and interests of the study populations (Question 55).

In sum, the NPRM proposals with respect to biospecimens and broad consent do not meaningfully advance subjects' autonomy interests; they furthermore come at a serious conceptual and logistical price. Contrary to the stated goals of the NPRM, these proposals will add administrative burdens with no assurance of enhancing subject protections. The NPRM does not, therefore, represent an improvement over the existing framework for research with biospecimens.

We recommend that the Common Rule agencies invest in further careful study of ways to honor and enhance subject autonomy in the context of biospecimens research. We urge the federal agencies to support the evaluation of alternative models of information sharing in terms of cost, rates of research participation, and subject satisfaction with consent. Such research might reveal that alternative regulatory solutions, such as a requirement to notify and provide an opt-out option, better address the ethical and practical complexity of the current research landscape. Or it might reveal that broader efforts to educate the public about biospecimen research would adequately enhance autonomy by fostering a shared conception of research participation as an obligation of all beneficiaries of the healthcare system. It is also possible that such study might reveal that a uniform approach under federal mandate will not meet all needs, and instead a system that allows policy decisions at the institutional level will better serve local populations, cultures, and research contexts.

Until such a comprehensive evaluation has been conducted, PRIM&R believes that the regulations governing research with biospecimens should remain unchanged.

III. Single IRB Mandate

Criticism has been leveled at the current practice of every institution involved in a mutli-center trial conducting its own IRB review. The NPRM introduces a radical regulatory change to the opposite effect: all US institutions engaged in cooperative research would be required to rely on a single IRB for review of each trial [§__.114(b)(1)]. This mandate has a simple and

appealing aim: to avoid redundant review as well as the inconsistencies and delays that arise when multiple IRBs review the same protocol. It is predicated on an assumption that the elimination of institution-based review will have no effect on the quality of review or on human subjects protections but will streamline review. No support is offered, however, for the conclusion that mandating the use of a single IRB in *all* multi-site research—rather than on a case-by-case basis—is the right policy.

The NPRM states that single IRB review will result in decreased administrative burden and increased efficiency, but the NPRM underplays the costs associated with organizing and implementing single IRB review, which, in many circumstances, will outweigh the projected benefits. For example, for every cooperative study, each institution's specific role and relative authority for study oversight must be negotiated and assigned. Further, absent IRB review at a participating site, investigators and human research protections programs will need to expend considerable effort and time to establish the means for inter-institutional information-sharing and cooperation. Institutions also need to agree on the specific methods by which each will ensure that protocols adhere to local law, community standards, privacy rules, training requirements, and conflict of interest policies, among other tasks. While standardized templates will provide some administrative shortcuts, each new multisite study will present a unique set of administrative challenges (Question 74). Rather than eliminating unnecessary administrative burden, reliance on single IRB review in many cases may give rise to unnecessary demands, delays, and distractions from the work of human subject protection.

To be sure, single IRB review may have advantages for particular multi-site studies, based on the number and types of institutions involved or the nature of the research (for example, when dealing with a rare condition where each site will accrue only a few subjects). Thus, in some circumstances, the advantages may outweigh the complications and costs involved in single IRB review. But the proposed regulatory changes fail to acknowledge that reliance on a single IRB will not always be advantageous. For instance, when the total number of institutions is small, when the scientific role at each institution is distinct (for example, institution A ascertains subjects and biological samples, while institution B conducts imaging procedures), and when population characteristics demand local consideration, review by each institution or by more than one IRB may be sensible (Question 77).

The Common Rule already permits institutions to rely on a single IRB, and to work with one another regarding the distribution of the costs of coordination. Likewise, as the National Institutes of Health (NIH) has shown, research funders can also insist that the institutions participating in certain multi-site research make use of a central IRB, with the features of the process and the selection of the central IRB tailored to the particularities of the study. No reason has been given for believing that a *regulatory mandate* to use a single IRB in every instance of cooperative/multi-site research is more advantageous than study-specific or institution-initiated use of a single IRB. Therefore, we recommend that the federal agencies encourage the development and evaluation of cooperative-review models and case-based

decisions about when reliance on a single IRB creates a favorable balance of efficiency and quality in review.

Furthermore, we foresee possible untoward consequences associated with routinely shifting the locus of ethical oversight and responsibility to other institutions or to commercial IRBs. Specifically, outsourcing of ethical review to numerous external entities may serve to diffuse institutional responsibility and undermine shared commitment to the standards that are fundamental to an institution's culture of accountability, integrity, and pride in its research. Over the past two decades, institutions have invested considerable effort to improve their human research protections programs, promote the ethical conduct of research, and increase their ability to conduct high quality review. This work often involves the development and dissemination of uniform policies and practices that reflect institutional consensus, as well as the enhancement of educational programming for individuals involved in human subjects protections. The proposed mandate may make such institutional efforts increasingly complex or diminish their impact as there will be significant heterogeneity in the way protocols are implemented within a single institution, given the institution's potential plethora of separate relationship with multiple external IRBs.

The problems associated with heterogeneity around research review are also likely to be reflected in the experience of investigators. Under the single IRB mandate, an institution's investigators will be accountable to the requirements of multiple external IRBs, their electronic systems for protocol submission, requirements for review, standard operating procedures, and ethical guidelines. For example, an investigator overseeing three cooperative research projects under the purview of three different external IRBs may have to apply and enforce differing rules related to assent or study exit criteria. Such variation across studies will add a layer of complexity that will predictably produce inadvertent compliance failures by investigators and institutions. The NPRM assumes that single IRB review will have no impact on the quality of human subjects protections; but whether or not it will is an open question that requires further careful study. PRIM&R encourages the Common Rule agencies to support such examination and to have in hand evidence about the actual costs and benefits before imposing such a requirement.

Finally, the NPRM, like the parallel policy recently promulgated by NIH, is vague about the criteria by which one institution or another or an independent IRB is to be selected as the single IRB by the funding agency or other sponsor. Absent a fully transparent methodology involving sponsors, investigations, and institutions, we are concerned that ethical considerations will lose priority to speed of review or cost-savings, among others. The criteria by which federal agencies will select the IRB on which all institutions will rely for a study should be established with public input before institutions are required to use a single IRB in a multi-site study, whether on an individual or across-the-board basis (Question 75).

IV. Exclusions and Exemptions

The preamble to the NPRM indicates that the revisions to the Common Rule are intended to respond to concerns that the current regulatory framework does not appropriately calibrate the level of review a study receives with the risk of harm it poses; this imbalance is said to result in administrative burdens without necessarily enhancing the protection of subjects. The NPRM makes two broad changes designed to address this problem: it defines a new category of "exclusions," activities that would not be subject to the requirements of the Common Rule [§___.101(b)], and it expands the existing category of exemptions (§___.104).

In general, PRIM&R supports the Common Rule agencies' efforts to better calibrate review and risk. Indeed, some proposals in the NPRM, such as the explicit exclusion of certain activities "deemed not to be research"[(§__.101(b)(1)], present a reasonable means of focusing the time and attention of IRBs on research more likely to pose significant risk. Nevertheless, we are concerned that decisions to exclude or exempt other categories of research, including some that have been excluded because they are "considered to be low-risk human subjects research" [(§__.101(b)(1)], are predicated on an overly narrow conception of research harm and a limited understanding of the purpose of ethics review.

Specifically, the NPRM indicates that certain activities are categorized as excluded or exempt because the primary ethical concerns associated with those activities are harms related to the inadvertent disclosure of private information. As a result, the NPRM posits that when appropriate privacy, confidentiality, and security safeguards are in place, IRB review is unnecessary. However, thoughtful ethics review requires the identification and consideration of a broader range of factors of concern to investigators, subjects, and communities. The emphasis on privacy to the exclusion of all else is less a recalibration than a dismissal of matters of fundamental ethical concern.

Comprehensive ethics review of the sort envisioned in the *Belmont Report* requires thoughtful and experienced individuals to weigh the benefits and harms of each research project in terms of beneficence, justice, and respect for persons. Consider, for instance, a study in which college-aged victims of sexual trauma suffering from post-traumatic stress disorder are interviewed about their experience. Under the proposal at §__.101(b)(2)(i), this study may not be subject to the regulatory requirements of the Common Rule if the data are not recorded in an identifiable manner *or* if the researcher determines that disclosure of "responses outside the research would not reasonably place the subject at risk of criminal liability or be damaging to the subject's financial standing, employability, reputation, educational advancement, or reputation" [§__.101(b)(2)(i)]. However, research only involving "interviews" often raises ethical questions beyond these privacy concerns, such as whether subjects will be recruited in a setting and in a manner that enables them to decline study involvement, whether subjects will receive sufficient information about the nature of the research interview before being asked to make a decision to participate, whether the interviewers are appropriately trained to work with victims of sexual violence, whether there

is a plan in place to address imminent risk associated with depression, substance use, or suicidal ideation if it emerges during the course of the interview, and whether the research is designed in a way that ensures its results will be useful.

Currently, research projects like this example may be eligible for an exemption under 45 CFR 46.101(b)(2). At most institutions, this means that an experienced IRB staff person will review the study to determine whether it meets the exemption criteria and to weigh any other regulatory or ethical considerations that the research may raise. Through this process, many of the considerations outlined above, as well as those related to ensuring subject privacy, are evaluated and institutional oversight is established. If the reviewer determines that the research raises significant concerns, it may be subject to further consideration or oversight.

The NPRM proposes to eliminate this process, which allows low-risk research that presents special concerns to be identified and that makes institutions aware of ongoing research activities. Besides minimizing institutional oversight, the NPRM would largely leave to investigators the responsibility for determining that their own research qualifies as "excluded" or "exempt." PRIM&R finds this to be problematic (Question 11). Certain categories of research, specifically the category described in §__.101(b)(2)(i), warrant greater oversight in order to ensure that IRB staff or members consider *all* factors that may contribute to a given study's ethical permissibility (Question 9). To that end, PRIM&R believes that the proposed exclusion categories should not be promulgated as written. Rather, the NPRM should reflect the reality that even ostensibly low-risk research activities can benefit from institutional oversight. Further, the regulatory language should make clear that institutions should have in place mechanisms for identifying and reviewing ethical considerations that such activities raise.

PRIM&R also believes that, as is current practice, exempt research should be subject to some level of institutional review and oversight. Furthermore, we encourage the Common Rule agencies to make clear that while certain types of research are excluded or exempt from the federal regulatory requirements, institutions are free to require all research conducted within their walls to undergo normal research review and oversight processes.

Both by assigning to individual investigators the responsibility of determining whether a proposed activity falls into one of the exclusion categories and by allowing investigators, or other individuals knowledgeable about a given study, to make a determination about whether the study is exempt [§__.104(c)] (using a to-be-developed "decision tool" from DHHS), the NPRM contradicts the current expectation—as it relates to exemptions—that "because of the potential for conflict of interest, investigators not be given the authority to make an independent determination that human subjects research is exempt."[2] On what

[2] Office for Human Research Protections. "Frequently Asked Questions: Who May Determine that Research is Exempt?" Department of Health and Human Services, 20 January 2011. Web. 12 December 2015.

ground are such basic changes proposed? On "the assumption that all investigators will be accurately determining whether their proposed activity is outside the scope of the Common Rule" (DHHS 2015, 53950). Such a leap of faith is hard to justify (Question 30).

The presumption behind the proposed rule change—that investigators will apply the rule accurately and free of the obvious conflict of interest (i.e., the opportunity to avoid the trouble of taking a proposal through IRB review)—is testable empirically, but no such evidence is provided. Alternatively, the rule change may be premised on the notion that, given that the types of research involved are generally low risk, it is of little or no consequence if an investigator makes an incorrect "exclusion" determination. This, too, seems to represent a great leap, as there is no way to know how often research that is not low risk will end up being judged by those wishing to conduct it to be excludable.

In light of the obvious potential for inaccurate and biased determinations, if researchers are given greater responsibility for determining which activities are and aren't research, and which aspects of research do and don't raise subject protection concerns, the fact that the NPRM does not require mechanisms to hold researchers accountable for protecting subjects seems particularly shortsighted. The NPRM needs to specify the minimum processes for holding investigators accountable regarding the accuracy or appropriateness of their decisions around risk and risk mitigation, consent, and the need for further oversight. (The next section elaborates on this point.)

Furthermore, if a category of excluded studies is to be created and the category of exempt research expanded, the Common Rule should explicitly mandate research ethics education for investigators. Consider, for example, the exemption category proposed in §__.104(d)(3) ("research involving benign interventions in conjunction with the collection of data from adult subjects through verbal or written responses...or video recording if the subject prospectively agrees to the intervention and data collection"). Absent adequate education in human subjects protections, how will investigators interpret whether "disclosure of the human subjects' responses outside the research would not reasonably place the subject at risk of criminal liability or be damaging to the subject's financial standing, employability, reputation, educational advancement, or reputation"? Or whether "subjects will find the interventions offensive or embarrassing"? A cautious investigator might not exclude any research that even hints at a disabling medical condition, HIV status, psychiatric disorder, non-heterosexual sexual orientation, or non-conforming gender identity, while a less conscientious or sensitive investigator could believe that such factors do not unnecessarily place subjects at risk.

Formal education in research ethics is essential for making many of the complex determinations outlined above. Without adequate education and training about how to identify issues that may create ethical concern, the proposed changes to the Common Rule

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http://www.hhs.gov/ohrp/policy/faq/exempt-research-determination/who-may-determine-that-research-is-exempt.html.

related to excluded and exempt research will result in investigators making markedly inconsistent decisions and exposing some subjects to risks that are certainly not "low" (Question 30).

Furthermore, should any final rule adopt the NPRM's proposals regarding the process for exclusions and exemptions, that rule must provide greater clarity with respect to investigators' obligations when overseeing excluded and exempt research. By definition some excluded and all exempt research involves human subjects. Therefore, it essential for the Common Rule to require investigators to inform all potential subjects that they are being asked to be part of a research study, that they can refuse to participate with no negative consequences, and that they can withdraw from the research at any time. This does not necessarily mean a consent form is required; what is needed is a conversation between the investigator and prospective subjects, the outcome of which can be recorded by investigators in their research notes, on survey forms, and so forth. This obligation, which is in line with the principles set forth in the *Belmont Report*, should be clearly communicated to investigators and mechanisms should be established for ascertaining their performance of this obligation and for holding accountable any investigators who fail to comply (Question 11).

Finally, the agencies' failure to provide for public review the proposed "decision tool" that is central to the assumption that investigators can be relied upon to make exemption determinations correctly is yet another indication that it would be premature to adopt the regulatory changes proposed in the NPRM. Moreover, a tool of appropriate sophistication to effectively characterize research as warranting exemption or requiring ethical review is very difficult to imagine.

V. Investigator Responsibilities

Across a number of proposals, the NPRM signals a decentralization of research protections and a shift away from the institution-wide, integrated system of subjects protections that currently characterizes the oversight of human subjects research. For instance, under the single IRB proposal, an institution's authority and ability to observe, monitor, and track research activities conducted within its walls would be less clearly defined, since individual investigators would need to coordinate with one or more outside entities the steps they must take to protect subjects. And under the proposals related to excluded and exempt research, institutions and their oversight bodies will largely be removed from the process of making determinations about whether a proposed activity is exempt. Instead, as mentioned above, individual investigators will assume sole responsibility for deciding when a given activity will be reviewed by the IRB.

In reference to excluded research, the NPRM states that: "All investigators performing excluded studies are expected to act in a way that is consistent with the principles outlined in the *Belmont Report*, even if the Common Rule does not impose requirements on excluded

work" (DHHS 2015, 53950). While welcome in concept, this language cannot be expected to have any meaningful impact on investigators since no mechanisms exist or are proposed in the NPRM for holding responsible investigators who fail to adhere to the *Belmont* principles. Lacking the direction and oversight of IRBs and institutions some investigators will be less likely to honor—and perhaps even to understand—their obligations to protect human subjects. In response to such concerns, many institutions and IRBs will probably attempt to develop their own policies and procedures for overseeing research that investigators have excluded from normal review, thereby adding complexity and inconsistency to the system.

To remedy these shortcomings and ensure that the rights and welfare of research subjects are safeguarded in the proposed world of diminished institutional involvement, the Common Rule should delineate specific investigator responsibilities as the Presidential Commission for the Study of Bioethical Issues and SACHRP, among other bodies, have recommended.[3,4] The inclusion of requirements for uniform and comprehensive ethics education, for judging investigators' adherence to the principles and practice of human subjects protections, and for imposing sanctions for failure to abide by those principles and practices, would align the Common Rule with Food and Drug Administration (FDA) regulations and promote a more robust culture of ethics within and across institutions.

VI. Informed Consent

A broad consensus exists that current practices for obtaining informed consent do not properly serve its original purpose: to facilitate an informed decision by prospective subjects as to whether or not to take part in research. In the absence of clinical standards or other countervailing influences, compliance and risk management have driven the development and use of consent forms that are too long and too complex to facilitate truly informed consent. Yet no solutions to this problem have become evident.

To address this issue, the NPRM includes new requirements that we interpret as an attempt to re-focus attention during consent on the presentation of the information that is most essential to each particular consent decision. Such efforts represent an important step in the right direction. Indeed, in past comments to DHHS and the FDA, PRIM&R has advocated for just such an approach.[5]

The NPRM proposes changes to the consent requirements that would require potential subjects to be provided with the "information that a reasonable person would want to have

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[3] Secretary's Advisory Committee on Human Research Protections. "Recommendations Regarding Investigator Responsibilities." Department of Health and Human Services, January 20, 2013. Web. 23 December 2015. http://www.hhs.gov/ohrp/sachrp/commsec/attachmentc-sec.letter19.pdf

[4] Presidential Commission for the Study of Bioethical Issues. *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: Presidential Commission for the Study of Bioethical Issues, December 2011.

[5] Public Responsibility in Medicine and Research. "RE: Docket Number HHS-OPHS-2011-0005, Advance Notice of Proposed Rulemaking on Human subjects Research Protections Published in the July 26, 2011 Federal Register." 6 October 2011.

in order to make an informed decision about whether to participate, and an opportunity to discuss that information." The proposed regulation also adds, "The information...must be organized and presented in a way that ...facilitates the prospective subjects understanding of the reasons why one might or might not want to participate" (DHHS 2015, 53970). Four fundamental enhancements are proposed: a standard for what information should be disclosed, a reference to the need for discussion during the consent process, a direct reference to a requirement that subjects must understand the relevant information, and an explicit statement that the organization and presentation of the consent information must facilitate this understanding. Each of these underscores the importance of the consent *process*, of engaging subjects, of assessing their understanding, and of attending to how information is organized and presented in the consent form and in the interaction with the subject. This regulatory language provides a foundation on which specific formal guidance on the informed consent process can be constructed. As such, we believe it may serve to inspire the development, evaluation, and dissemination of much needed new consent practices. As a next step, to ensure these changes are truly operationalized, PRIM&R believes the Common Rule agencies should fund or otherwise incentivize the creation, study, or use of novel techniques to improve informed consent (Question 60).

We doubt, however, the value of the proposed requirement to post on a publicly accessible federal website the final version of the consent form for all clinical trials conducted or supported by a federal department or agency [§__.116(h)(1)]. Given the sheer volume of such trials, the website is likely to be cumbersome and difficult to navigate. In addition, a form that is presented in isolation from the protocol for which it was created and from the process by which it was employed is unlikely to serve an instructive purpose. Thus, the mandate to post consent forms will likely result in additional costs and administrative burdens without corresponding gains for subject protections.

As we have suggested elsewhere, we recommend that the Common Rule agencies invest in the evaluation of such a practice before mandating compliance in regulation. In the interim, researchers, IRBs, and sponsors, should be encouraged to establish mechanisms to voluntarily share informed consent forms, as well as other resources used throughout the consent process when such materials have been shown to improve the research enterprise (Question 60).

VII. Conclusion

Without question, an improved and modernized system of human subjects protection will better serve both research subjects and science. But neither the scientific community nor the public can have confidence that better, consistent, and ethically sound practices will emerge from the regulatory changes proposed by this NPRM.

To summarize:

- The proposals to redefine research with biospecimens as human subjects research and require broad consent for biospecimen use do not represent an improvement over the current system; they are unlikely to further the interests of subject autonomy and may create new obstacles to research participation. Alternative models need to be studied if the rules on the use of biospecimens and personally identifiable data are to respect subjects' wishes and protect their interests while also allowing researchers to access a wide range of biospecimens and data. The proposed regulatory change lacks adequate warrant in the absence of a more careful evaluation of their implications and feasibility.

- Mandating reliance on a single IRB in all cases of multi-site research is overly rigid. The Common Rule should continue to permit research institutions and research funders to develop and evaluate cooperative reliance models and to make case-by-case decisions regarding when the use of a single IRB will best balance efficiency and quality of review in light of the particularities of a given multi-site study or trial.

- Many of the revisions related to the new category of exclusions and the expansion of exemptions unduly reduce the protection of human subjects, reflect an oversimplification of what is entailed in meaningful ethics review, and lack essential requirements for investigator education about the ethics of research and the grounds for excluding or exempting studies from the requirements of the Common Rule.

- As the locus of responsibility for human research protections shifts away from institutions, the role of the individual investigators grows and along with that must come regulations to define and enforce investigators' responsibilities to protect human subjects.

- We endorse the idea that information must be presented to potential subjects in a manner that facilitates understanding, but question the value of the requirement that informed consent forms must be posted on a federal website.

Sound policymaking does not rely on risky experimentation of the sort the NPRM embodies. Thus, at this time, we do not believe efforts to finalize the NPRM as it is should move ahead. Rather, the many shortcomings in this attempt at comprehensive reformulation—a few of which are catalogued in this letter—suggest a better way forward: thoughtful, incremental revisions of individual Common Rule provisions that reflect careful study and input along the way from the research protections community, researchers, and the public.

Thank you for the opportunity to comment on this very important rulemaking effort. We hope the Common Rule agencies will step back and reconsider not just the specific proposals

within the NPRM but its entire approach to regulatory change. The stakeholders that look to PRIM&R for leadership would be greatly reassured to see the Common Rule agencies following a rule-revision process that was more careful and considered and that aired issues and possible solutions in an open and consultative fashion. The results of the current approach, as embodied in the present NPRM, are not reassuring, either with respect to the adequacy, efficacy, and ethical soundness of the changes now on the table, or to the ability of the agencies to reassess and revise the Common Rule if, as we expect, many of the regulations proposed in the NPRM would not produce the promised beneficial results.

If you have any questions or require any further information, please feel free to contact PRIM&R through its executive director, Dr. Elisa A. Hurley at (617) 423-4112 or ehurley@primr.org.

Respectfully Submitted,

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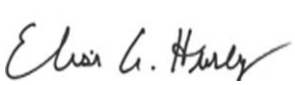

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cc: Board of Directors